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10/574,438	06/25/2007	Raymond Nadeson	210174.401USPC	9722

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EXAMINER	
JAGOE, DONNA A	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,438	NADESON ET AL.	
	Examiner	Art Unit	
	Donna Jagoe	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *43-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *43-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments filed March 19, 2009 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claims 43-50 are pending in this application.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 43-45 and 48 are rejected under 35 U.S.C. 102(e) as being anticipated by Klose et al. U.S. Patent No. 6,916,486 B2.

Klose et al. teach an analgesic composition (see abstract) for treatment of neuropathic pain (column 6, lines 55-59) comprising flupirtine (column 3, line 28) and other opioid analgesics such as buprenorphine, dextromoramide, dextropropoxyphen, diamorphine, fentanyl, alfentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, papaveretum, pentazocine, pethidine, codeine and dihydrocodeine. (column 3, line 28, and claims 5, 6, 11 and 12) for use in treatment of an animal, including a human (column 1, lines 19-20). Claims 11 and 12 of the patent describes the method of administering **at least one** systemic acting analgesic to an animal wherein the analgesic is selected from the agents listed above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 47 is rejected under 35 U.S.C. 103(a) as being unpatentable over Klose et al. U.S. Patent No. 6,916,486 B2 and Devulder at al. (U).

Klose et al. teach an analgesic composition (see abstract) for treatment of neuropathic pain (column 6, lines 55-59) comprising flupirtine and other opioid analgesics such as buprenorphine, dextromoramide, dextropropoxyphen, diamorphine, fentanyl, alfentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, papaveretum, pentazocine, pethidine, codeine and dihydrocodeine. (column 3, line 28, and claims 5, 6, 11 and 12) for use in treatment of an animal, including a human (column 1, lines 19-20). Claims 11 and 12 of the patent describes the method of administering **at least one** systemic acting analgesic to an animal wherein the analgesic is selected from the agents listed above.

Klose et al. does not teach the dose instantly recited in claim 47.

Devulder et al. teach the dose of flupirtine for treatment of neuropathic (central) pain is 300-600 mg/day. The instant claim is drawn to 0.5mg/kg to about 20 mg/kg of body weight. Translating the dose of Devulder et al. to mg/kg based on an average 80 kg human the dosage would be 3.75 mg/kg[1] to 7.5 mg/kg[2]. This dosage amount is encompassed by the claimed amount of 0.5 mg/kg to about 20 mg/kg. A prior art reference that discloses a range encompassing a somewhat narrower claimed range is sufficient to establish a prima facie case of obviousness." *In re Peterson*, 315 F.3d 1325, 1330, 65 USPQ2d 1379, 1382-83 (Fed. Cir. 2003). See also *In re Harris*, 409 F.3d 1339, 74 USPQ2d 1951 (Fed. Cir. 2005).

It would have been made obvious to one of ordinary skill in art at the time it was made to employ 0.5 mg/kg to about 20 mg/kg of flupirtine in the composition combined with another opioid agent to treat neuropathic pain motivated by the teaching of Klose et al. who teaches the combination for treatment of neuropathic pain and the teaching of Devulder et al. who teaches that the dosage of flupirtine for central (neuropathic) pain is 300 to 600 mg/day (approximately 3.75 mg/kg to about 7.5 mg/kg).

Claim 46 is rejected under 35 U.S.C. 103(a) as being unpatentable over Klose et al. U.S. Patent No. 6,916,486 B2 and Perovic et al. (V).

Klose et al. teach an analgesic composition (see abstract) for treatment of neuropathic pain (column 6, lines 55-59) comprising flupirtine and other opioid

[1] 300 mg / 80 kg = 3.75 mg/kg
[2] 600 mg / 80 kg = 7.5 mg/kg

analgesics such as buprenorphine, dextromoramide, dextropropoxyphen, diamorphine, fentanyl, alfentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, papaveretum, pentazocine, pethidine, codeine and dihydrocodeine. (column 3, line 28, and claims 5, 6, 11 and 12) for use in treatment of an animal, including a human (column 1, lines 19-20). Claims 11 and 12 of the patent describes the method of administering **at least one** systemic acting analgesic to an animal wherein the analgesic is selected from the agents listed above.

Klose et al. does not disclose absence of overt sedation of opioids in the presence of flupirtine.

Perovic et al. teach that flupirtine is a clinically safe compound with drowsiness reported in only 10% of cases (page 373, column 2). Since the dosage of the opioid is not disclosed, then the claim encompasses an almost negligible amount of opioid and as such overt sedation would not occur since it is dose related.

It would have been made obvious to one of ordinary skill in art at the time it was made to employ a non sedating combination of flupirtine and an opioid motivated by the teaching of Perovic et al. that flupirtine caused drowsiness in only 10 % of cases combined with the well known fact that sedation of opioid analgesics is dose related and since the claims do not disclose the dosage, they encompass a negligible amount of opioid.

Claims 49 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al. Patent Application Publication US 2003/0082214 A1 and Cleary (Cancer Control, 2000 (U)).

Williams et al. teach compositions for treating pain such as neuropathic pain (see abstract, paragraphs 2, 9, and 58) such as cancer with nerve invasion (neuropathic cancer) (paragraph 58) comprising administration of a NMDA receptor antagonist such as flupirtine (paragraph 113) and opioids such as alfentanil, buprenorphine, oxycodone, papaveretum, papaverine, pentazocine, codeine, etc. (paragraph 149). It does not teach the specific cancer types such as those recited in instant claim 50.

Cleary teaches that cancer pain can have a neuropathic component (page 122, column 2 "character"). It further identifies specific cancers for which such neuropathies occur, such as colon cancer, non-small cell lung cancer and multi-organ system failure associated with cancer (page 121 column 2 bridging to page 122). Cleary also discloses that although opioids are the mainstay of cancer pain management, adjunct therapy is recommended. Adjuvant medications may result in an decrease in opioid dose with an associated decrease in side effects and adjuvant therapy is often useful with opioids in the treatment of neuropathic pain. (page 127, column 2).

Thus the claims fail to patentably distinguish over the state of the art as represented by the cited references.

Accordingly, for the above reasons, the claims are deemed properly rejected and none are allowed.

Response to Declaration

The Declaration under 37 CFR 1.132 filed March 19, 2009 is insufficient to overcome the rejection of claims 43-45 and 48 based upon 35 U.S.C. 102(e) as being anticipated by Klose et al. U.S. Patent No. 6,916,486 B2 as set forth in the last Office action because:

The instant claims are drawn to administration of flupirtine in combination with other opioid analgesics such as fentanyl, oxycodone, codeine, dihydrocodeine, dihydrocodeinone enol acetate, morphine, alfentanyl, hydrocodone, dihydromorphone, methadone, morphine, papaveretum, pentazocine, etc. The instant claims do not exclude topical administration. Declarant's arguments mainly state that the transdermal formulations of Klose et al. do not work because a higher plasma level of flupirtine is required to produce a therapeutic level, however, there is no requirement for a specific dose in the instant claims and as recited supra, the instant claims do not exclude topical administration.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence fails to outweigh the evidence of the anticipatory reference.

Response to Arguments

Regarding instant claims 49 and 50, these new claims were submitted on September 22, 2008. The official office action with the first action on the merits was based on the amended claim set submitted June 25, 2007. It appears that the official

office action and the claim set mailed on September 22, 2008 crossed in the mail. New claims 49 and 50 are considered supra.

Applicant's arguments, see page 8, filed March 19, 2009, with respect to claims 44-47 have been fully considered and are persuasive. The rejection of claims 44-47 under 35 USC §112, second paragraph has been withdrawn. Applicant 's response that the structure of instant claim 43 is flupirtine is sufficient to support the assertion of antecedent basis in the claims.

Applicant asserts that Klose et al. fails to anticipate the subject matter of the instant claims because the claimed subject matter doesn't disclose with sufficient specificity, the specific combination of flupirtine and the recited opioids for treating neuropathic pain. In response, Klose et al. teach treatment of diseases or conditions including neuropathic pain (column 6, lines 55-59) and further teach flupirtine, and other opioid analgesics (column 3, lines 15-30) and teach administering at least one systemic acting analgesic to an animal in an **effective** amount (see abstract, column 3, lines 44-48). "Applicant's attention is directed to the MPEP at §2131.02 (see "A Reference That Clearly Names the Claimed Species Anticipates the Claim No Matter How Many Other Species Are Named"), which states, "A genus does not always anticipate a claim to a species within the genus. However, when the species is **clearly named**, the species claim is **anticipated** no matter how many other species are additionally named. *Ex parte A,* 17. USPQ2d 1716 (Bd. Pat. App. & Inter. 1990) (The claimed compound was named in a reference which also disclosed 45 other compounds. *The Board held that the comprehensiveness of the listing did not negate the fact that the compound claimed*

was specifically taught. The Board compared the facts to the situation in which the compound was found in the Merck Index, saying that 'the tenth edition of the Merck Index lists ten thousand compounds. In our view, each and every one of those compounds is described' as that term is used in 35 U.S.C. 102(a), in that publication.'). Id. at 1718. See also *In re Simvaramakrishnan,* 673 F.2d 1383, 213 USPQ 441 (CCPA 1982)."

Regarding the rejection of instant claim 46 over Klose et al. and Perovic et al and claim 47 over and Klose et al. and Devulder et al. under 35 USC § 103(a), Applicant asserts that the references fail to teach, suggest or motivate a person skilled in the art to use flupirtine in combination with the recited opioids for treating neuropathic pain with any expectation of success, let alone with a reasonable expectation of success. Applicant states that the Examiner has relied on "generalized boilerplate claim preamble language". The meaning of this statement is unclear to the Examiner. The abstract of Klose et al. teach that the invention provides a method for administering **at least** one systemic acting analgesic to an animal. Column 3, lines 44-48 and claims 11 and 12 of the patent also clarify that at least one analgesic is administered (more than one can be administered together). Applicant states that Perovic et al. is not supported by any real evidence in the assertion that flupirtine was reported to cause drowsiness **in only 10% of cases**. Applicant has supplied the McMahon reference as evidence that this 10 % is not supported. Upon inspection of the reference, it is found that the assertion is indeed supported. McMahon states that adverse experiences occurring in flupirtine clinical studies have been minimal in incidence, nature and degree, with **drowsiness** being the

most frequently reported reaction (**approximately 10%**) (see abstract) meaning that only 10% report drowsiness. Consequently, this argument does not raise an issue of material fact. Applicant also submits Hlavica et al. because it makes no mention of flupirtine causing drowsiness in only 10% of cases. In response, it is immaterial that the Hlavica et al. reference makes no mention of drowsiness or the lack of drowsiness. Regarding the amount of opioid, since there is no dosage recited, one can conclude that any amount is contemplated, including negligible amounts.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-0576. The examiner can normally be reached on Monday through Friday from 8:00 A.M. - 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Donna Jagoe /D. J./
Examiner
Art Unit 1614

June 2, 2009

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614